

### REMARKS

In the most recently received non-final Official Action, the Examiners have rejected pending claims 11-12 respectively under a variety of different bases. Initially, the Examiners have rejected the pending claims under 35 U.S.C. 112, first paragraph, as being non-enabling for a defined family of short-length PR-39 derived oligopeptides. In addition, the Examiners have rejected the pending claims under 35 U.S.C. 112, second paragraph, as being vague in language. Moreover, the Examiners have rejected the pending claims under the judicially created doctrine of double patenting over the claims of co-pending USSN 09/276,868. Finally, the Examiners have rejected the pending claims under 35 U.S.C. 103(a) as being unpatentable over Ross *et al.*, U.S. Patent No. 6,133,233.

In response, applicants have amended presently pending independent claim 1; and enclosed a copy of a previously submitted Terminal Disclaimer. By this claim amendment, enclosure, and the discussion presented hereinafter, applicants believe they have overcome and obviated each basis for rejection stated by the Examiners in the most recent received non-final Official Action.

Applicants and their undersigned attorney wish to state their intentions clearly. It is applicants' express desire and purpose to advance the prosecution of this application on the merits, and not to delay or hinder its progress. It is a matter of formal record that this invention and patent application was filed on October 25<sup>th</sup>, 1999; and the prosecution file history to date, now over five years in duration, is amply littered with a broad range of questionable distractions, diversions, and digressions of varying kinds.

It is the applicants' undersigned attorney's earnest hope that the Examiners will be able to keep an open mind and have an unprejudiced approach concerning the issues now in dispute; and also that the Examiners will be able to recognize and appreciate the merits of a presented position which is opposite and stands in contradiction to the Examiners' stated point of view. On this premise, applicants will now address and review each of the different substantive bases for rejection stated by the Examiners in the instant Official Action with regard both to its legal requirements and the relevant factual circumstances.

## I. A Continuing Unresolved Matter

As a continuing unresolved matter, applicants respectfully state

that the Examiners of record again have failed even to acknowledge as well as failed to respond to applicants' formally presented and explicitly stated position concerning the basis and nature of the Examiners' self-imposed election of species.

Applicants, in their Request For Continuing Examination submitted March 30, 2004 as well as in their Response submitted July 23<sup>rd</sup>, 2003 [to the Non-final Official Action mailed May 30<sup>th</sup>, 2003], have stated and maintained that: (i) The Examiners of record have unilaterally and without applicants' consent imposed an election of species; and, (ii) the Examiners have chosen to misinterpret and wrongly presume that applicants' identification of SEQ ID NO:3 as one representative embodiment of the PR-39 derived oligopeptide family constitutes an election of species for that sequence alone for prosecution on the merits. Applicants again affirm that the Examiners' actions in this regard are erroneously based and completely unjustified.

Applicants also again respectfully submit and maintain that the Examiners actions and decisions are directly opposite to and contradict the Examiners' explicit statements and formal positions presented at page 4, 2<sup>nd</sup> paragraph of the Office Communication mailed April 7, 2003 - which demanded a Restriction Requirement, but did not ask for

any election of species as such. Applicants' formal Response mailed April 15<sup>th</sup>, 2003 not only traversed the Restricted Requirement in its entirety, but also explicitly stated that Applicants did not then and do not now make any election of species whatsoever [Page 2, 2<sup>nd</sup> paragraph of the Reply mailed April 15, 2003].

The Examiners have clearly misread and misinterpreted applicants' written remarks and positions; and decidedly ignored and evaded from the Examiners' stated stance and explicitly expressed position. Moreover, it appears that the Examiners continue to believe that they can ignore and evade from their prior stated stance and legal position in the Office Communication mailed April 7<sup>th</sup>, 2003; and that the Examiners apparently presume that they can arbitrarily alter and completely reverse their earlier-stated view and position whenever it suits them, at the Examiners' whim.

Despite these attempts at evasion, the Examiners' previously stated position is a matter of formal record; and remains factually and legally binding upon the Examiners as the "law of the case" under the legal doctrine of estoppel as well as by the legal constraints imposed by the prosecution file history to date. The Examiners' formally stated prior stance is not merely a minor item or trivial footnote which can be ignored and forgotten whenever it suits the Examiners' convenience.

Applicants' position is therefore directly opposite and contrary to the Examiners' present stance: The Examiners are factually constrained and are legally obligated to maintain a consistent position. Moreover, the Examiners have an overt duty and affirmative responsibility to meet and keep their word and commitments as stated.

For these reasons, applicants request that the Examiners of record reconsider their inconsistent position and formally reinstate dependent claims 13 and 14 respectively as presently pending claims in this application.

## II. Applicants' Presently Claimed Invention

Before the question of whether or not the Specification text provides sufficient enablement for pending claims 11 and 12 can be properly answered, it is useful first to summarize briefly the essence of the instant invention in order to identify what applicants' invention actually is as well as to separate and distinguish the defined invention from what it is not.

Applicants' invention is claimed specifically as a "PR-39 derived oligopeptide family". This term, "PR-39 derived oligopeptide family", is defined by amended independent claim 11 as a combination of requisite elements and particular limitations; and comprises a family whose individual members cause a selective inhibition of protease-mediated degradation in-situ after introduction intracellularly to a viable cell. The full membership of

the PR-39 derived oligopeptide family is presently defined by amended independent claim 1.

In comparison, one particular preferred embodiment and member of this family of short-length oligopeptides is defined by dependent claim 12; and is a precisely recited sequence of 15 amino acid residues. For reasons previously stated above, only the family definition recited by amended claim 11 and the preferred 15 residue length embodiment recited by amended claim 12 constitute the claims presently pending in this application.

In addition, it will be noted that the wording of presently amended independent claim 11 recites the commonly shared characteristics and properties for the short-length amino acid residue length structures comprising the membership of this family of peptides; and that claim 11 delineates a circumscribed membership which is size-limited, is functionally specific, and is structurally related as a family of pharmacologically active oligopeptides. The commonly shared characteristics and properties of the PR-39 derived oligopeptide family are overtly stated and individually set forth as requisite elements and specific limitations by amended independent claim 11 and are recited as specific residues in sequence by amended dependent claim 12.

It will be appreciated also that amended independent claim 11 explicitly sets forth six specific requirements for each member constituting this family

of derived oligopeptides. These requirements include: that the maximum length of each oligopeptide be from about 8-25 amino acid residues in length; that each oligopeptide begin with the sequence "Arg-Arg-Arg" at its N-terminal end; that each oligopeptide be devoid of the amino acid sequences "Pro-Pro-X-X-Pro-Pro-X-X-Pro" and " Pro-Pro-X-X-X-Pro-Pro-X-X-Pro" where X is any amino acid; that each peptide be able to be introduced intracellularly to a viable cell; that each oligopeptide be able to interact selectively in-situ with such proteasomes as are present within the cytoplasm of the cell; and that each oligopeptide be able to alter markedly the proteolytic degradation activity of these proteasomes such that a an increased expression of an identifiable peptide occurs in-situ as a consequence.

Amended dependent claim 12 presents the 15 amino acid residue length restatement of this broad definition; a recitation which complies fully and completely with the stated requirements of amended independent claim 11. Accordingly, amended claims 11 and 12 respectively present an accurate and precise recitation of applicants' inventive subject matter as a whole.

### III. The Rejection Under 35 U.S.C. 112, 1<sup>st</sup> Paragraph, Enablement

The Examiners have rejected claims 11-12 under 35 U.S.C. 112, first paragraph, because the Specification text allegedly fails to provide sufficient information which would enable one skilled in the art to make and practice

applicants' invention as presently claimed.

The substance of the Examiners' view and position is stated at pages 3-4 in the most recently received Official Action. After restating almost the entirety of the language recited by pending claim 11, the Examiners then present their rationale for rejection within a single sentence, the relevant portion of which is reproduced below:

"...In view of the above, those skilled in the art are unlikely to accept the data as being correlatable to SEQ ID NO:3, a 15 amino acid residue and a family of PR-39 derived oligopeptides whose members individually cause a selective inhibition of proteasome-mediated degradation for at least one identifiable peptide in-situ after introduction intracellularly to a viable cell...."  
[page 3, lines 6-10 of the instant Official Action].

In response to the Examiners' stated rationale, applicants and their undersigned attorney respectfully submit the following:

First, the Examiners have failed to present a *prima facie* case which is their exclusive burden and legal obligation.

Second, the Examiners have conducted an evaluation which does not conform to the correct and proper objective legal standards regarding enablement as prescribed by statute and the governing caselaw decisions.

Third, the Examiners have failed to appreciate properly the totality of factual content disclosed by the Specification text, and have failed to give proper credence to the quality and quantity of information presented by the written disclosure.



Each of these major failures and errors will be demonstrated and explained in detail.

A. The Examiners' Duty To Present A *Prima Facie* Case

As regards the Examiners' rejection of the pending claims under Section 112, first paragraph, it is applicants' position that this rejection is legally insupportable and without foundation in view of *In re Marzocchi* [169 USPQ 369 (1971) and the case decisions recited herein]. Before the Examiners may reject any claims in this manner, the Examiners must meet and satisfy the respective burdens placed on them by the requirements of *In re Marzocchi*, which states in pertinent part as follows:

"As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that such sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling.

In the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings and pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. In any event, it is incumbent upon the Patent Office, whenever a rejection on this

basis is made, to explain why it doubts the truth of the accuracy of any statement in a supporting disclosure and to backup assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." [emphasis in the original text; 169 USPQ at 369-370].

Given the single sentence rationale stated at page 3, lines 6-10 of the instant Office Action, it clear that the Examiners have failed to present any impartial evidence or unbiased reasoning which is inconsistent with either the disclosure of the Specification text or the scope of the pending claims. Moreover, the Examiners have failed to explain why they doubt the objective truth or accuracy of any statement in the Specification text ,aside from their own subjective belief that "...others skilled in the art would be unable to practice the invention as claimed without undue experimentation and with a reasonable expectation of success" [page 3, lines 17-19 of the instant Office Action].

Equally important, a mere statement by the Examiners - that the examples given within the present Specification text are too limiting or are not representative of a broad class of compositions as claimed - is not legally sufficient and does not fulfill the legal burden of presenting and factually supporting a *prima facie* case of non-enablement. Rather, the Examiners are themselves required to explain in objective terms why they doubt the truth of any statement in the disclosure before the Examiners can assert that one or more particular embodiments embraced by the claims cannot be used in

the manner indicated. In each instance, the Examiners must provide acceptable evidence or offer a factually supported rationale for presenting such a challenge [In re Dinh-Nguyen, 181 USPQ 46 (CCPA 1974); In re Bowen, 181 USPQ 48 (CCPA 1974)].

In addition, the Examiners are not permitted to base their rejection upon a merely conclusive statement that the practice of the invention would be beyond the skill of the person ordinarily skilled in this art [In re Brebner, 173 USPQ 169 (1972)].

#### B. The Legal Standards Of Section 112, 1<sup>st</sup> Paragraph

##### *The controlling caselaw decisions:*

It will be noted that the caselaw decisions to date have repeatedly and particularly emphasized that the first paragraph of Section 112 does not require a specific example of everything lying within the scope of a broadly stated claim [In re Anderson, 176 USPQ 331 (CCPA 1973)]. The caselaw decisions routinely stress that not even a single working embodiment, nor an illustration, nor a working example of the claimed invention is required to exist within the Specification text in order to meet and fully comply with the enablement provisions of Section 112 [In re Stephens, 188 USPQ 659 (CCPA 1976); In re Barr, 170 USPQ 330 (CCPA 1971)].

Thus, the fact that a Specification text may be devoid of even one

working or illustrative example is itself without legal significance; and it is well established that illustrative examples or empirical data and the like are not legally necessary in order to have an enabling disclosure [In re Borkowski, 164 U.S.P.Q. 642 (CCPA 1970)]. Accordingly, the presence or absence of even a single illustrative or working example does not of itself provide any legal basis or support to explain why a Specification text is not enabling or to explain why the scope of the enablement is not commensurate with the scope of protection sought by the pending claims.

In each and every instance of rejection, therefore, the Examiners have the legal burden of providing specific reasons to explain why the Specification is not enabling as well as to make clear why the scope of the enablement is not commensurate with the scope of protection sought by the pending claims [In re Armbruster, 185 USPQ 152 (CCPA 1975); In re Angstadt, 190 USPQ 214 (CCPA 1976)].

In this regard, applicants respectfully remind the Examiner that he has presented multiple working examples; and has stated explicitly how to use each of these within the Specification text. Applicants, as a matter of law, are not required to present evidence of how to make and use each and every possible embodiment lying within the broad class of compounds defined by the pending claims.

*Practice of the claimed invention without "undue experimentation":*

The Examiners' rejection on the basis of a non-enabling disclosure also carries with it the sub-issue of whether applicants' Specification is sufficient to enable one of ordinary skilled in the art to practice the claimed invention without "undue experimentation".

Applicants note that the Specification text provides multiple examples of the member compositions and includes at least one specific empirical demonstration which shows the commonly-shared selective inhibition characteristics of the PR-39 derived oligopeptide membership. Applicants again point out that the Examiners alone have the exclusive legal burden of giving reasons, supported by objective facts, as to why the Specification disclosure is not enabling as well as for believing that the disclosure entails 'undue experimentation' [In re Strahilevitz, 668 F.2d 1229 (CCPA 1982)]. In the absence of any cogent evidence or objective reasons, there is no proper basis to support a non-enablement rejection and the Examiners have not fulfilled their legal obligation and burden [In re Morehouse, 545 F. 2d 162 (CCPA 1976)].

It is especially noteworthy also to recognize that no court of law has ever held that evidence of the necessity for any experimentation, however slight, is sufficient to prove that 'undue experimentation' is required. To the contrary, it is expected and intended that the ordinarily skilled practitioner

perform some experiments, particularly when the invention is a composition of matter, in order to determine the most optimal dosages, the preferred routes of administration, and an efficacious duration of treatment [In re Eynde, 178 USPQ 470 (CCPA 1973)].

The objective determination of what constitutes "undue experimentation" in any given instance therefore requires the application of the standard of reasonableness, having due regard for the nature of the invention as claimed and the state of the pertinent art. This test is not merely quantitative since a considerable amount of experimentation is legally permissible. Thus, if such experimentation is merely routine, or if the Specification text provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed, then such experimentation is not "undue". The key and essential word, therefore, is always "undue" and not "experimentation" [In re Angstadt, 190 USPQ 214 (CCPA 1976); Atlas Powder Company vs. E.I. DuPont DeNemours & Co., 224 USPQ 409 (Fed. Cir. 1984); In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988)].

Accordingly, it is only when the degree of experimentation becomes "undue" that one fails to satisfy the 1<sup>st</sup> paragraph of Section 112; and there has been no objective evidence or reasoning presented to date which supports such an extreme situation for the instant Specification text. Thus, there is therefore no underlying basis for the Examiners now stating that

"undue" experimentation is required [In re Geerdes, 180 USPQ 791 (CCPA 1974)].

*Additional enablement standards for the Examiners:*

Nothing more than objective enablement is required as a matter of law; and it is irrelevant whether this quantum of information is provided through a broadly written description and disclosure, or by illustrative examples, or by working experiments with observed empirical data [In re Wright, 27 U.S.P.Q. 2d 1510 (1993)]. Thus, there is no meaningful difference for enablement purposes whether: (i) merely a broad description in meaningful detail is disclosed by a Specification text; or (ii) a series of illustrative hypothetical examples within a variety of circumstances is provided; or (iii) a series of test experiments with resulting empirical data and supported conclusions in any degree, quality or format is presented. Any written disclosure of information and descriptive detail in any of these presentation forms is legally adequate and factually sufficient to satisfy the enablement requirement.

In addition, as a matter of long-established legal principle, there is no requirement under 35 U.S.C. 112, 1<sup>st</sup> paragraph that an inventor correctly set forth, or even know, how or why the claimed invention works or functions [Newman v. Quigg, 11 U.S.P.Q.2d 1340 (Fed. Cir. 1989)].

Moreover, it is axiomatic that an inventor need not even comprehend the scientific principles upon which the practical effectiveness of his invention rests [Fromson v. Advance Offset Plate, Inc., 219 U.S.P.Q.2d 1137 (Fed. Cir. 1983)]. Accordingly, therefore, no legal basis or duty of any kind exists for the written disclosure of a Specification to provide any explanation, or any understanding, or even any theory of why the claimed invention works or how the claimed invention functions.

Furthermore, the presence of experimental details or other descriptive statements within a disclosure that a particular physiological phenomenon was observed and experimentally evaluated are not deemed to be "intrinsically suspect" simply because the underlying biomolecular basis for the empirical observation cannot be predicted or explained [In re Cortright, 49 U.S. P.Q.2d 1464 (Fed. Cir. 1999)]. Thus, the Examiners cannot overtly state or even suggest that the enablement requirement legally demands that applicants prove the mechanism of action involved or the nature of a function/structure relationship to account for the observed physiological activity and the consequential result caused by a defined composition of matter.

The enablement requirement of Section 112, 1<sup>st</sup> paragraph, also does not require that the disclosure of the Specification convince any person (including the Examiners) that the assertions, information, and knowledge



contained therein are proven correct to the point of absolute certainty [In re Robins, 429 F.2d 452 (CCPA 1970)]. There is thus no legal requirement in law that the Examiners become completely persuaded; or become a committed follower; or be a true supporter of the scientific model, theory or premise upon which an invention is based or of any mechanism of action upon which the invention relies.

### C. The Factual Errors Of The Examiners

As applicants have shown and documented previously herein, the Specification text not only describes in detail the commonly shared characteristics and properties of the PR-39 oligopeptide family at page 25, lines 1-22; but also sets forth at page 26, lines 1-32 multiple illustrative examples and preferred embodiments of the membership which constitutes the PR-39 derived oligopeptide family as such.

In addition, the commonly shared characteristics and properties of the PR-39 derived oligopeptide family described in detail at page 25 and 26 of the Specification text are overtly restated and individually set forth; and this antecedent description corresponds and directly correlates with the requisite elements and specific limitations recited by amended independent claims 11 and 12 respectively.

Equally important, in opposition and contradiction to the Examiners' stated view, these specified traits and attributes for the membership constituting the PR-39 derived oligopeptide family as a whole also have been experimentally illustrated and empirically validated. Such evidence is disclosed by Experiment 6 and the use of PR-11, as described at page 46, lines 1-24 of the Specification. This working example and representative embodiment amply evidences and empirically demonstrates the requisite structure, function, and pharmacological activity for the entire PR-39 derived oligopeptide family membership as defined by amended independent claims 11 and 12 respectively.

It is important also for the Examiners to recognize and acknowledge that the other experiments and empirical results described within the Specification text at pages 40-45 constitute probative evidence of the traits and attributes of the PR-39 derived oligopeptide family as a whole; and such evidence clearly exemplifies the utility and capabilities for the more limited membership of the PR-39 derived oligopeptide family defined by amended independent claims 11 and 12 respectively.

Applicants and their undersigned attorney therefore respectfully submit and affirm that an objective review and evaluation of the range of antecedent description and the variety of illustrative details disclosed by the Specification text reveals all the necessary knowledge and information

concerning the structure, attributes and traits of the oligopeptides defined by amended independent claims 11 and 12 such that any ordinarily skilled practitioner could identify, prepare and use any chosen member of the PR-39 derived oligopeptide family as a whole.

#### D. The Prejudicial Error In The Examiners' Evaluation

Applicants respectfully submit and affirm that all the essential aspects of the invention defined by amended claims 11 and 12 respectively are disclosed in written descriptive detail; are structurally and functionally characterized by experiment and empirical data; and are revealed in multiple illustrations and embodiments by the Specification text. In addition, applicants have clearly shown that the Specification text provides specific parameters of, guidance for and valuable insights to choosing, preparing and making any chosen embodiment of the PR-39 derived oligopeptide family – whenever the ordinarily skilled person in this technical field wishes to do so. Given this totality of information, guidance and insight now existing within the Specification text, anyone ordinarily skilled in this art would have no need or use for a redundant recitation directed to a structure to function/activity relationship in order to make and use applicants' defined invention for its intended purpose.

Furthermore, applicants respectfully submit that the manner of making and using the present invention is revealed in full and explicated in depth by the range and variety of the experiments and empirical data disclosed by the Specification text. Thus, the practitioner ordinarily skilled in this art could easily prepare and utilize without major difficulty many different embodiments of the entire PR-39 derived oligopeptide family as a whole from the limited membership defined by amended independent claims 11 and 12 respectively.

Applicants also submit and maintain that the Specification text provides an abundance of detailed description and informative information as to how to make and use analogues of PR-39 shorter than 26 amino acid residues in length - which is the subject matter as a whole defined by the presently pending claims. So long as the each member of the PR-39 derived oligopeptide family is structurally an analog of native PR-39, is pharmacologically active, and can interact with proteasomes in the specified manner to achieve the desired result, there is no practical need for nor any informational value in a theoretical function/activity to structure relationship either in the disclosure or within the recited definition of applicants' invention.

In summary, applicants respectfully submit and maintain that the Examiners have failed to adhere to or comply with the above-identified proper legal standards when conducting their assessment and evaluation of the claims pending in the present application. Instead, the Examiners have improperly insisted upon more working examples; and peremptorily required more information – all of which would constitute merely ordinary and routine experiments - to provide, at most, an empirical showing of non-essential variables for the relevant art. None of the Examiners' demands for such information, even if acquiesced to, would be of unusual or additional benefit to the practitioner in this field, given the quantity and quality of information and knowledge disclosed by the Specification text presently to the ordinarily skilled practitioner in the art.

For these reasons, applicants submit and affirm that the Examiners have made multiple factual and legal errors regarding the enablement requirement for applicants' invention as presently claimed. Accordingly, on the basis of all the foregoing, applicants request that the Examiners reconsider their position and withdraw this ground of rejection against the presently pending claims.

#### IV. The Rejection Under 35 U.S.C. 112, 2<sup>nd</sup> Paragraph

The Examiners have rejected claims 11 and 12 under 35 U.S.C. 112, 2<sup>nd</sup> paragraph as being vague and indefinite in language. The Examiners' position is based on two different alleged flaws. These are: (i) The use of the phrase "A family of PR-39 derived oligopeptides" within the preamble of the pending claims. The Examiners' stated view is that "...This is indefinite as to the metes and bounds of the oligopeptide/invention the applicant is claiming" [page 4, lines 4-5 of the instant Office Action]; and (ii) Applicants' recited claim of "...a peptide of less than 26 amino acid residues in length does not adequately define the metes and bounds of the invention, as the invention(s) can be from about 8 to about 25 amino acids in length...." [page 4, lines 16-18 of the instant Office Action]. In response, applicants direct the Examiners' attention to the following.

(α) Applicants' invention is claimed specifically as a "PR-39 derived oligopeptide family". This term, "PR-39 derived oligopeptide family", is defined with particularity at page 25, lines 1-22 of the Specification; is compared to the corresponding term "PR-39 peptides group" at page 24, lines 7-23 of the Specification; and is contrasted to the umbrella term and category title "PR-39 oligopeptide collective" at page 26, lines 35-39 and page 27, lines 1-7 of the Specification.

Clearly, the phrase "PR-39 derived oligopeptide family" is properly defined, fully described, and compared in meaning with other similar nomenclature and terms completely by the Specification text. The connotative and denotative meaning of this phrase is therefore unambiguous, exact and specifically understood in context. Thus, there is no reason or basis why this phrase can or should be deemed to be vague or indefinite by the Examiners.

(β) Applicants have chosen to acquiesce to the Examiners' stated view that "a peptide of less than 26 amino acid residues in length" does not adequately define the metes and bounds of the invention; and have amended independent claim 11 to recite -- a peptide ranging from about 8 to about 25 amino acid residues in length --. This amendment distinctly points out the size range of the oligopeptides

Accordingly, as regards the language of the pending claims as a whole, the essential inquiry is to determine whether the language of the pending claims do, in fact, set out and circumscribe a particular area or subject matter with a reasonable degree of precision and particularity. It is here where the meaning of the words and language employed to define the invention is analyzed; not in a vacuum, but always with regard to the teachings of the prior art and within the particular description, use or context disclosed by the Specification as it is understood and interpreted by one

possessing ordinary skill in the pertinent art [In re Angstadt, 190 USPQ 214 (CCPA 1976)].

Finally, applicants note that each of the terms used in pending claims respectively is well understood; is not subject to numerous definitions and interpretations; and that there is no discrepancy, no confusion, and no ambiguity with regard to the antecedent descriptive basis and support provided by the Specification text. Rather, the language of the presently pending claims as a whole read on subject matter which is completely disclosed and enabled by the Specification text. Moreover, each recited element of the pending claims is explicit and clearly stated; and employs wording which sets forth and circumscribes the particular subject matter area with the requisite reasonable degree of precision and particularity [In re Moore, 169 USPQ 236 (CCPA 1971)].

For these reasons, applicants respectfully submit that each and every claim now pending satisfies the requirements of precision, clarity, and particularity required by the second paragraph of 35 U.S.C. 112. Accordingly, applicants respectfully request that the Examiners reconsider their stated position and withdraw this ground of rejection against the presently pending claims.



## V. The Double Patenting Rejection

The Examiners have provisionally rejected pending claims 11 and 12 under the judicially created doctrine of double patenting over claims 11 and 12 of copending USSN 09/276,868.

Applicants and their undersigned attorney, however, do not understand why this rejection basis has been presented at this time - especially in view of the fact that such a rejection basis was previously presented by the Office Action mailed May 30<sup>th</sup>, 2003; and the issue was resolved completely at that time via the submission of a formal Terminal Disclaimer and fee which was enclosed as part of the substantive Response mailed July 23<sup>rd</sup>, 2003. In addition, applicants direct the Examiners attention to pages 13 of applicants' Response mailed July 23<sup>rd</sup>, 2003 which addressed the issue directly; and also explicitly noted the enclosure of a formally executed Terminal Disclaimer whose text was fully in compliance with the requirements of 37 C.F.R. 1.32(c).

To evidence further the previous occurrence of these facts and events, applicants enclose herewith a copy of the Terminal Disclaimer executed and submitted on July 23, 2003, which was presented to the Examiners as an enclosure to the substantive Response mailed on that date. This executed document constitutes a legal commitment which permanently joins and forever links the two copending patent applications together for the duration

of their legal lives. Moreover, via this previously submitted Terminal Disclaimer document on July 23<sup>rd</sup>, 2003, applicants at that time properly legally overcame and completely obviated the provisional double patenting rejection basis in its entirety.

Unfortunately, it appears that the Examiners are not aware that these facts and events did previously occur; and are not cognizant that this double patenting basis for rejection was previously presented and was completely resolved at an earlier time. The Examiners also have apparently mislaid and overlooked the very existence and legal effect of the previously submitted formal Terminal Disclaimer and fee which was enclosed as part of the substantive Response mailed July 23<sup>rd</sup>, 2003.

Accordingly, for all these reasons above, applicants respectfully request that the Examiners reconsider their stated position, recognize the nature of their error, and withdraw this ground of rejection against the presently pending claims.

#### VI. The Rejection Under 35 U.S.C. 103(a)

The Examiners have rejected claims 11 and 12 respectively under 35 U.S.C. 103(a) as being anticipated by the Ross *et al.* reference, U.S. Patent No. 6,133,233. The reasons and rationale explicitly stated by the Examiners at pages 6-7 of the instant Official Action to justify this rejection are:

- (i) Ross *et al.* teach an in vivo method of reducing reperfusion injury in a mammal which administers into the mammal's blood stream an effective amount of proline/arginine rich peptide; and
- (ii) Ross *et al.* disclose SEQ ID NO:4, a 14 amino acid peptide which is a 95% query match with SEQ ID NO:3 (claim 12).

Applicants respectfully affirm and maintain that the Examiners are factually incorrect and legally in error as regards the issue of non-obviousness under 35 U.S.C. 103(a); and are particularly wrong concerning the quality and quantity of the information said to be taught and suggested by the disclosure of the Ross *et al.* '233 patent. Each of these errors is reviewed in detail hereinafter.

*A. The legal standard for determining non-obviousness:*

As a matter of long established law, the proper legal basis and standard for determining obviousness under 35 U.S.C. 103(a) is as follows: Where applicant's claimed subject matter can be rejected as obvious in view of a single reference or a combination of prior art references, a proper analysis must consider inter alia two factors: (1) whether the prior art of record would have suggested to those of ordinary skill in the art that they

should make and use the claimed article or claimed composition; and (2) whether the prior art would also have revealed that in so making and using, those of ordinary skill would have a reasonable expectation of success [In re Dow Chemical Company, 5 USPQ 2d 1529 (Fed. Cir. 1988)].

Note that both the suggestion and the reasonable expectation of success must be found within the prior art reference itself and not in applicant's disclosure [In re Vaeck, 20 USPQ 2d 1438 (Fed. Cir. 1991)]. Equally important, the same inquiry must be carried out in the context of a purported "obvious modification" of the prior art information. The mere fact that the prior art might be modified in the manner suggested by the Examiner does not make that modification obvious unless the prior art itself suggested the desirability of the modification [In re Fritch, 23 USPQ 2d 1780 (Fed. Cir. 1992) and the references cited therein].

Applicants therefore respectively submit that the Examiners' stated views and conclusions in the instant Official Action do not satisfy the objective legal standard required for a conclusion of obviousness.

*B. The factual content of the Ross et al. '233 patent:*

Applicants respectfully submit and maintain that the information provided by the Ross et al. '233 patent must be read as actually written and be understood in context as the person ordinarily skilled in this field would

do. A careful reading and proper review of the disclosure of the '233 patent reveals only the following.

1. The Ross *et al.* invention is described and defined solely as an in-vivo method of reducing reperfusion injury in a mammal resulting from temporary occlusion of a blood vessel and subsequent reperfusion thereof [Column 1, lines 17-20; Column 2, lines 22-26; claim 1]. The explicitly stated object and sole goal of the Ross *et al.* method is to inhibit the indices of reperfusion injury - *i.e.*, inhibiting the production of reactive oxygen species, inhibiting neutrophil adherence to endothelium, and inhibiting extravasation of neutrophils as a result of reperfusion [Column 1, lines 28-31 and 42-63].

2. The Ross *et al.* method is directed solely and exclusively to reducing reperfusion injury in a mammal which results from the reperfusion of a temporarily occluded blood vessel. To achieve this purpose, the disclosed method clearly and overtly demands two things of the user: a means of access to the vascular blood system of the mammal having a temporarily occluded blood vessel; and a mode of administration for delivery of a suitable composition able to reduce reperfusion injury within the blood stream of the mammal's vascular system after the temporary occlusion in the blood vessel has been removed.

For this reason, the Ross *et al.* method as described and defined by the '233 patent explicitly sets forth two carefully recited manipulative steps: administering into the mammal's bloodstream a reperfusion injury-reducing amount of a peptide having up to about 50 amino acid residues, at least 65 % of which are proline and arginine residues; and allowing the peptide administered to the blood to come into effective contact with the temporarily occluded blood vessel in order to minimize the degree of reperfusion injury [Column 2, lines 22-32; Claim 1].

3. The Ross *et al.* method is clearly described as being dependent upon an ability to counteract the effects of oxygen-derived free radicals which are released during reperfusion injury, after the temporary occlusion of a blood vessel has been removed. These oxygen-derived free radicals are said to be the primary mechanism of oxidative damage to cell structures; and are caused by reactive oxygen species (such as a superoxide ion) which are central to these events during reperfusion of temporarily occluded blood vessels [Column 1, lines 47—54 and 64-67]. For this reason also, the experiments and empirical results analytically measured the generation of reactive oxygen intermediate species [Column 5, lines 52-60].

4. A number of markedly different compositions of matter are deemed to be suitable for administration to the living mammal for reducing reperfusion injury resulting from temporary occlusion of a blood vessel by Ross *et al.* These include Bac 5, Bac 7, C7 and PAF [see Fig. 5].

Included among these also are the "synducins" – that is, PR-39 polypeptide and its longer-length analogues which were known previously to induce the expression of proteoglycans in mesenchymal cells. The structure of the "synducins", PR-39 polypeptide and its longer-length analogues, are expressly incorporated by reference into the Ross *et al.* Specification via PCT Publication WO 96/09322, which provides the following additional points of information:

(i) The PR-39 amino acid sequence must be employed at a minimum size as a 39 amino acid residue sequence in order for the desired biological activity to be demonstrated;

(ii) The entire 39 amino acid sequence of PR-39 can be part of a larger sized molecule, such as a fusion protein or when a mobilized to an inert substrate or targeted using a specific ligand, as part of a longer length protein;

(iii) The entire PR-39 peptide and any of its longer length analogues are collectively identified as "synducins" — all of which are characterized by a specific biological activity and a particular mechanism of action;

(iv) The "synducin" characteristic biological activity and specified mechanism of action are the inducement of syndecan-1 and syndecan-4 expression on the surface of mesenchymal cells. This is achieved via specific inducement of syndecan-1 and syndecan-4 mRNA within cells; or by an increase in the level of cell surface heparan sulfate and rapid uptake of such heparan sulfate into mesenchymal cells to a saturation level; and

(v) To be biochemically active, "synducins" must include a specific and lengthy amino acid sequence which is: Pro-Pro-X-X-Pro-Pro-X-X-Pro and Pro-Pro-X-X-X-Pro-Pro-X-X-Pro, where X is any amino acid.

5. The description and evidence disclosed by the Ross *et al.* '233 patent, however, increases the minimal structural requirements for the peptide compositions to be administered in-vivo for reducing reperfusion injury after temporary occlusion of a blood vessel. In particular, to be suitable for use in the Ross *et al.* method, the composition demonstrably must be:

(a) A peptide preferably comprising up to 50 amino acid residues, wherein at least 60 percent of such residues are proline and arginine residues. In preferred forms, the proline and arginine residues will constitute from 65-80 percent of the total residues in the composition [Column 2, lines 32-55]; and



(b) A peptide which has at least one amino acid sequence of -PXXP-, and preferably at least four such sequences of -PXXP-, wherein P is a proline residue and X is any amino acid residue. Moreover, these peptides should have one or more basic residues within six residues (and preferably within three residues) from both the starting and terminal proline residues of the —PXXP- sequence. Thus, each peptide composition suitable for administration should contain a sequence such as  $X_1X_2X_3X_4X_5X_6PXXPX_7X_8X_9X_{10}X_{11}X_{12}$  where such or all of the  $X_1$ - $X_{12}$  amino acid residues are basic residues [Column 2, lines 56-76; Column 3, lines 1-11]. It is explicitly noted that the requirement for the —PXXP- structure is critical for activity if such a peptide structure is to be effective in-vivo for reducing reperfusion injury [Column 3, lines 12-34].

6. The disclosure of the '233 patent also presents several experiments and empirical data which demonstrate the value of PR-39 and its structurally related peptides in the inhibition of the indices of reperfusion injury after temporary occlusion of a blood vessel. These experiments clinically evaluate the activity of PR-39 polypeptide and other peptides via: the generation and quantitative measurement of reactive oxygen release, as shown by Example 1; measurements of neutrophil adherence to postcapillary venules; preventing the loss of vascular integrity, as shown by Example 2; and

inhibition of superoxide anion production and neutrophil chemotaxis, as shown by Example 3 [Columns 5-8 respectively].

Also, as expressly stated therein, pretreatment of living subjects prevented loss of vascular integrity resulting from reperfusion injury and blocking reperfusion-induced production of reactive oxygen, neutrophil adhesion and loss of vascular integrity [Column 6, lines 62-76]. Similarly, such peptides are found to be chemotactic for neutrophils when used alone, but are capable of acting as inhibitors when used in combination [Column 8, lines 63-76].

This factual summary presents the total useful information and data which would be recognized as being taught and/or suggested by the disclosure of the Ross *et al.* '233 patent to persons of ordinary skill in the technical field.

*C. The absence of a factual basis for the Examiners' rejection:*

There are many major factual differences and substantive distinctions between applicants' invention as defined by amended independent claim 11 and the disclosure of the Ross *et al.* '233 patent reference.

(i). The Ross *et al.* '233 patent disclosure does not generally teach the administration of PR-39 and related peptides to a patient as such; and, in

particular, does not suggest the existence of a peptide able to be introduced intracellularly to a viable cell. To the contrary, the '233 patent is explicitly specific in teaching that the Ross *et al.* method is not only expressly limited to reducing reperfusion injury in a mammal resulting from temporary occlusion of a blood vessel and subsequent reperfusion thereof; but also is a technique exclusively restricted to inhibiting the clinical indices of reperfusion injury – *i.e.*, to inhibit production of reactive oxygen species, to inhibit neutrophil adherence to endothelium, and to inhibit extravasation of neutrophils.

In comparison, applicants' invention, as defined by amended independent claim 11, is a family of PR-39 derived oligopeptides employed solely and exclusively for selectively inhibiting proteasome-mediated degradation within the cytoplasm of a viable cell, an unquestionably different function and objective. Thus, there is no relationship, technical or otherwise, existing between the stated goals and purposes of the Ross *et al.* method as disclosed and applicants' recited invention; and there is no nexus of any kind between the Ross *et al.* methodology and applicants' defined compositions, each of which is intended to achieve results and consequences which are radically different and remote from one another.

(ii). The Ross *et al.* method overtly requires access to and a direct administration to the vascular blood system of the mammal in order to reach the cells within a temporarily occluded blood vessel; and also must deliver a prechosen peptide composition capable of reducing reperfusion injury within the blood stream of the mammal's vascular system after the temporary occlusion in the blood vessel has been removed.

In comparison, applicants' invention makes no such explicit demands; nor requires any such limitations or restrictions as to what organs in the mammal are targeted or how the in-vivo delivery and administration of the desired compounds is to be achieved. Furthermore, as presently amended, applicants' family of oligopeptides need only be able to be introduced intracellularly to a viable cell for selective inhibition of proteasome-mediated degradation.

(iii). The Ross *et al.* method is clearly dependent upon a capability to counteract the effects of oxygen-derived free radicals which are released during reperfusion injury, after the temporary occlusion of a blood vessel has been removed. As expressly disclosed by the '233 patent, these oxygen-derived free radicals are generated during reperfusion of temporarily occluded blood vessels; are released by the reperfused vascular system into

the blood stream; and are the primary cause and mechanism of oxidative damage to vascular cell structures during reperfusion.

In contradistinction, applicants' claimed invention has nothing to do with counteracting the effects of oxygen-derived free radicals; is unconcerned with reperfusion injury as such; and is not restricted to the vascular system of mammals having temporarily occluded blood vessels.

Rather, the intended targets of applicants' claimed compositions are entirely different - *i.e.*, viable cells lying within the living subject whose intracellular proteasomes interact with peptides and mediate peptide degradation as a customary event and routine metabolic pathway; and constitute those cells whose proteasome interactions with a member of the PR-39 oligopeptide collective will result in at least part of the proteolytic activity mediated by these proteasomes becoming selectively altered such that a marked inhibition of peptide degradation occurs in-situ. Clearly, the vascular system of mammals having temporarily occluded blood vessels of the Ross *et al.* method are notably and distinctly different in comparison to applicants' targeted cells

(iv). There is no overlap or similarity between the manipulative steps comprising the Ross *et al.* method in comparison to applicants' claimed compositions. The '233 patent reference patent explicitly administers into

the mammal's bloodstream a reperfusion injury-reducing amount of a peptide having up to about 50 amino acid residues, at least 65 % of which are proline and arginine residues; and it is these formulated peptides which, after being administered to the blood stream, come into effective contact with the temporarily occluded blood vessel in order to minimize the degree of reperfusion injury in-vivo.

In comparison, the family of PR-39 derived oligopeptides recited by amended independent claim 11 precisely recites structural properties and biochemical characteristics which do not set forth or share any of the explicitly demanded elements and limitations required by the Ross *et al.* process.

(v). The minimal structural demands for any peptide intended for use in the Ross *et al.* method are rigorous and explicit. These include a demand for a 60% - 65% proline/arginine residue content; and a need for multiple —PXXP- sequences within the peptide structure.

In comparison, applicants' claimed invention does not demand any particular amino acid residue content and does not require elaborate minimal structural moieties such as multiple —PXXP- sequences in order to provide demonstrable activity and utility for the PR-39 oligopeptide collective.

(vi) Equally important, applicants' claimed family of PR-39 derived oligopeptides affirmatively specifies and requires wholly different elements and limitations which are completely unknown within, are not described by, and are not suggested in any way by the disclosure of the '233 reference. These are: a peptide able to be introduced intracellularly to a viable cell; a peptide able to interact selectively with the proteasomes present within the cytoplasm of said targeted collection of cells such; and a peptide able to alter markedly the proteolytic degradation mediated by the proteasomes against at least one identifiable peptide such that an increased expression of the peptide occurs in-situ. Clearly therefore, the structural elements of applicants' claimed invention and the requisite manipulations of the Ross *et al.* method are not are not similar and do not share anything in common.

(vii). The entirety of the Ross *et al.* method is directed to a clinical demonstration and effecting a therapeutic effect which includes a blocking of reperfusion-induced production of reactive oxygen-derived intermediate species; a reduction of neutrophil adhesion and emigration; and a decrease in the loss of vascular integrity. No other kind of result or intended outcome is desired or suggested and no other type of evidence or proof exists within or is implied by the disclosure of the '233 reference.

In contradistinction, applicants' claimed invention does not rely upon a reduced production of oxygen, nor require a reduced neutrophil adhesion and emigration effect, nor demand an improvement of vascular integrity. The structural elements and specific limitations recited by applicants' claims are thus unknown and unrelated to the Ross *et al.* consequences and effects.

*The Examiners' multiple errors of judgement:*

( $\alpha$ ) Applicants respectfully submit and affirm that the Examiners do not have any factual or reasoned basis to support a rejection based upon obviousness in view of the quantity and the quality of facts and information taught or suggested by, or fairly inferable from the '233 patent. Applicants have factually demonstrated via probative evidence that the Ross *et al.* method is radically different and remote from applicants' claimed invention; and that the disclosure of the '233 patent is unconcerned with and unrelated to the goals and compositions necessary to practice applicants' claimed invention.

( $\beta$ ) Applicants also respectfully affirm and maintain that there is no substantive information, no significant facts, and no meaningful suggestion whatsoever for using the PR-39 polypeptide and its related peptides other than for the reducing the clinical indices of reperfusion injury, as explicitly described by the '233 patent disclosure. None of the requisite elements and



specific limitations recited by the manipulative steps of applicants' claimed invention can be found or inferred, either expressly or inherently, within the disclosure of the '233 patent.

(γ) Furthermore, as applicants have demonstrated herein, the absence of any congruent or similar descriptive detail and the lack of any relevant factual overlap unequivocally and categorically demonstrates that none of the requisite elements or specific limitations required by applicants' claimed invention can be recognized as being present or inferable from the totality of information and data provided by the '233 patent reference by persons of ordinary skill in this technical field. Thus, in accordance with established legal precedent and standards, where the requisite elements and specific limitations of applicants' claimed invention are not presented or suggested within the '233 patent in such a degree that a person of ordinary skill would expect or foresee them - then no factual support for rejection exists within the disclosure of the '233 patent and there is no legal justification at all for a rejection based upon obviousness.

(δ) Applicants maintain also that the Ross *et al.* '233 patent of record does not teach and could not suggest to those of ordinary skill in the art that they should prepare and use the compositions defined by claims

and 11 and 12 respectively. The '233 patent of record also has been demonstrated to show that, even if the ordinary practitioner had thought of making or using applicants' claimed compositions, those of ordinary skill in this field would not have any reasonable expectation of success. Accordingly the subject matter as a whole defined by amended independent claims 11 and 12 is unique and has substantial patentable merit.

In summary, applicants respectfully submit and affirm that the Examiners' stated views and position concerning the '233 patent are incorrect in substance and are not factually supported. Moreover, owing to this lack of evidentiary supporting facts, the Examiners have no legal basis or rationale for concluding that applicants' claimed invention is either obvious or lacks patentable merit. Accordingly, there is no legal justification or legal support – as noted by the relevant caselaw decisions presented herein - for the Examiners' belief that applicants' claimed invention is either expected or predictable by the disclosure of the '233 patent reference.

For all these reasons, applicants respectfully submit that the Examiner's reliance and use of the Ross *et al.* '233 patent fails blatantly as a factual reference; and that there is no legal support for a conclusion of obviousness under 35 U.S.C. 103(a). Accordingly, applicants request that

the Examiners reconsider their stated position and withdraw this ground of rejection against the presently pending claims.

*In sum*, applicants have addressed the each individual basis of rejection stated in the most recently received non-final Official Action forthrightly and objectively. In applicants' view, each issue has been evaluated, acted upon, and resolved completely. Accordingly, for these reasons, applicants respectfully submit and affirm that amended claims 11 and 12 now pending are therefore now allowable.

In view of the above discussion and detailed review, applicants believe that this case is now in condition for allowance and reconsideration is respectfully requested. The Examiners are invited to call applicants' undersigned attorney should they feel that such a telephone call would further the prosecution of the present application.

Respectfully submitted,

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